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Original

Influence of the body mass and visceral adiposity on glucose metabolism in obese women with Pro12Pro genotype in PPARgamma2 gene

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Abstract

Introduction: **Glucose metabolism may be altered in obesity and genotype for PPAR 2 can influence this variable.**

Objective: **To evaluate the influence of body mass (BM) and visceral adiposity (VA) in glucose metabolism in morbid obese women with Pro12Pro genotype.**

Methods: **Were selected 25 morbidly obese women. Groups were formed according to body mass index (BMI) [G1: 40-45 kg/m² (n = 17); G2: > 45 kg/m² (n = 8)]. Anthropometric, glycemia and insulinemia assessments (fasting, 60 and 120 minutes after high polyunsaturated fatty acids meal) were carried out. The insulin resistance (IR) and insulin sensitivity (IS) were assessed by HOMA-IR and QUICKI respectively.**

Results: **G2 had higher BMI and waist circumference, compared to G1, impaired fasting glucose, low IS and higher IR. The postprandial glucose was normal, but there was a higher insulin peak one hour after the meal in G2.**

Conclusion: **Increased BM and VA were associated with worse glucose metabolism suggesting metabolic differences between morbid obese with Pro12Pro genotype.**

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Key words: *Obesity. Body mass index. Glucose metabolism. Insulin resistance. PPARgamma.*

INFLUENCIA DE LA MASA CORPORAL Y DE LA ADIPOSIDAD VISCERAL EN EL METABOLISMO DE LA GLUCOSA EN MUJERES OBESAS CON EL GENOTIPO PRO12PRO EN EL GENE PPARGAMMA2

Resumen

Introducción: **El metabolismo de la glucosa puede estar alterado en la obesidad y el genotipo del gene PPAR 2 puede influir en este variable.**

Objetivo: **Evaluar la influencia de la masa corporal (MC) y de la adiposidad visceral (AV) en el metabolismo de la glucosa en mujeres con obesidad de grado 3 con el genotipo Pro12Pro.**

Métodos: **Se seleccionaron 25 mujeres con obesidad de grado 3. Se formaron grupos de acuerdo con el índice de masa corporal (IMC) [G1: 40-45 kg/m² (n = 17), G2: > 45 kg/m² (n = 8)]. Fueron hechas evaluaciones antropométricas, de la glucemia y de la insulinemia (en ayunas, 60 y 120 minutos después de la comida rica en ácidos grasos poliinsaturados). La resistencia a la insulina (RI) y sensibilidad a la insulina (SI) fueron evaluados por el HOMA-IR y QUICKI, respectivamente.**

Resultados: **G2 tuvieron mayor índice de masa corporal y circunferencia de la cintura, en comparación con G1, peor glucemia en ayunas, baja SI y alta RI. La glucosa postprandial fue normal, pero hubo un pico de insulina más alto una hora después de la comida en G2.**

Conclusión: **El aumento de la MC y de la AV se asociaron con peor metabolismo de la glucosa lo que sugiere diferencias metabólicas entre obesos de grado 3 con el genotipo Pro12Pro.**

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Palabras clave: *Obesidad. Índice de masa corporal. Metabolismo de la glucosa. Resistencia a la insulina. PPARgamma.*

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Abreviattions

BM: Body mass.
BMI: Body mass index.
bp: Base pairs.
C: Cytosine.
FURJ: Federal University of Rio de Janeiro.
G: Guanine.
HOMA-IR: Homeostasis Model Assessment-Insulin Resistance.
IR: Insulin resistance.
IS: Insulin sensitivity.
MUFA: Monounsaturated fatty acids.
PCR-RFLP: Polymerase chain reaction-restriction fragment-length polymorphism.
PPAR: Peroxisome proliferator-activated receptor.
PPARγ2: Peroxisome proliferator-activated receptor isoform gamma 2.
PPRE: Peroxisome proliferator response element.
PUFA: Polyunsaturated fatty acids.
QUICKI: Quantitative Insulin Sensitivity Check Index.
SFA: Saturated fatty acids.
TEE: Total energy expenditure.
TZDs: Thiazolidinediones.
VA: Visceral adiposity.
WC: Waist circumference.

Introduction

Obesity is considered one of the most serious public health problems throughout the world and results in overload on health services with an increasing demand for the treatment of other chronic diseases such as type 2 diabetes mellitus and cardiovascular disease.[1] It is a complex disease of multifactorial origin, with a strong influence from hereditary and environmental factors.[2]

Although it has polygenic characteristics, studies have emphasized the significant contribution of the adipogenic transcription factor, peroxisome proliferator-activated receptor *(PPAR)* isoform γ2 *(PPARγ2)* in lipogenesis.[2,3,4]

The PPARs belong to a superfamily of nuclear hormone receptors,[5] constituting a subfamily of three isoforms: *PPARα, PPARγ* and *PPARβ/δ*, which perform essential functions in regulating the lipid metabolism.[6,7] The *PPARγ* is presented in three subtypes (γ1, γ2 and γ3), which are expressed in different tissues.[7] The expression of *PPARγ2* occurs mainly in adipose tissue[6,8], being related to adipogenesis[3,6] and insulin sensitivity (IS).[9,10]

These transcription factors require activation from natural ligands to act on target genes, which include long-chain polyunsaturated fatty acids (PUFA), derived from oxidized lipids and eicosanoids; or synthetics, which include lipid-lowering and antidiabetic drugs, such as thiazolidinediones (TZDs), which have a high affinity for *PPARγ*.[5,7]

Genetic variants of *PPARγ2* have been identified, among which, Pro12Ala polymorphism, which is characterized by the replacement of cytosine (C) to guanine (G) in codon 12, with substitution of proline for alanine in the polypeptide sequence (Pro12Ala and Ala12Ala).[11]

Studies are being conducted to elucidate the effects of the wild-type genotype (Pro12Pro) and of the Ala variant allele in the *PPARγ2* gene, however, there is still no consensus on the results.[3,9,12] It is suggested that in the presence of the Pro12 homozygous genotype, the activation of the gene by agonists is associated with the expression of enzymes involved in the capture and transport of fatty acids, resulting in increased adipogenesis and decreased concentrations of plasma free fatty acids. As a result, there is less fat accumulation in liver and muscle tissues, favoring IS in these tissues.[13] However, in Ala allele carriers, there is lower affinity of the *PPARγ*-ligand complex with the peroxisome proliferator response element (PPRE) of target genes[12], which can result in less effective stimulus, and consequently, lower accumulation of adipose tissue.[9] Moreover, the relationship of this polymorphism with IS remains controversial.[3,9,12]

Insulin resistance (IR) is characterized by decreased effectiveness of insulin to stimulate glucose uptake in skeletal muscle and in adipose tissue.[14] This morbidity predisposes individuals to several chronic diseases, including hypertension, type 2 diabetes mellitus, dyslipidemia, ischemic heart disease, as well as providing generalized atherogenic activity. Among the etiologic factors for IR, in addition to previously reported genetic factors, there is the excess of body fat, especially visceral fat deposition.[1]

Obese people with less visceral adipose tissue were found to have normal glucose tolerance when compared to lean controls. Obese people with a high accumulation of visceral adipose tissue, however, showed an increase in their glycemic response to an oral glucose load which was measurably higher than in obese people with less visceral adipose tissue or in nonobese controls. Major differences were also noted in the plasma insulin response to the oral glucose load. These comparisons show that viscerally obese people represent a subgroup of obese patients with the highest glycemic and insulinemic responses to an oral glucose challenge and that they are at the highest risk of developing type 2 diabetes mellitus.[15]

Our aim was to evaluate the influence of body mass and visceral adiposity on glucose metabolism in fasting and postprandial glucose in morbidly obese women with genotype Pro12Pro in *PPARγ2*, considering the relationship of obesity with other chronic diseases associated with IR and the role of *PPARγ2* gene in adipogenesis and IS.

Materials and methods

Casuistry

We conducted a cross-sectional study of non-randomized and non-controlled intervention with 25 morbidly obese adult women (22-48 years old).

The study was approved by the Research Ethics Committee of the University Hospital Clementino Fraga Filho, of Federal University of Rio de Janeiro (FURJ) (research protocol N. 116/05). All volunteers signed the consent form before starting the search, as established by Resolution nº 196/96 of the National Health Council.

The inclusion criteria considered were: adult women with a family history of obesity, lack of menopause, and BMI equal to or greater than 40 kg/m^2.[16]

The study excluded women in situations of smoking, presence of cardiovascular diseases, chronic kidney disease, diabetes mellitus and/or other chronic diseases, infectious diseases, pregnant women, nursing, users of lipid-lowering, hypoglycemic agents, diuretics, antidepressants, antihypertensives, and drugs supplements and/or herbal remedies for weight loss, dieting for weight loss in the last four weeks, or weight loss greater than 3 kg in the last month.

Study design

We assessed the usual dietary intake in order to eliminate the influence of this variable in the parameters studied. Dietary intake was estimated using dietary records for three days, two days being typical and one atypical. The analysis of the chemical composition of the diets was performed using the Food Processor software version 12 (Esha Research, Salem, USA, 1984), after the adjustment for the typical Brazilian diet.

In the clinical trial, the volunteers were presented to the Laboratory of Clinical Analysis of Pharmacy College/FURJ at 7am after an overnight fast of 12 hours for the first blood sample for the biochemical (total cholesterol and fractions, triglycerides, glucose and insulin) and molecular (*PPARγ2* genotype) assessments. The anthropometric assessment was performed immediately after.

A high n-6 PUFA meal was administered orally. After one and two hours, blood samples were collected to assess glucose and insulin concentrations.

The volunteers were divided into two groups according to BMI, with G1 composed of women with BMI between 40 and 45 kg/m^2 (n = 17) and G2 composed of women with a BMI equal to or greater than 45 kg/m^2 (n = 8).

Biochemical measurements

Lipemia and glycemia were carried out at Laboratory of Clinical Analysis of Pharmacy College/FURJ. For total cholesterol, HDL-cholesterol and triglycerides measurements the commercial kits CHOLESTEROL Liquiform (Labtest Diagnostica SA, Brazil), HDL CHOLESTEROL (Labtest Diagnostica SA, Brazil) and triglycerides Liquiform (Labtest Diagnostica SA, Brazil) were used, respectively.

LDL-cholesterol and VLDL-cholesterol concentrations were determined using the Friedewald equation.[17]

The reference values used for triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol levels were < 150 mg/dL, < 200 mg/dL, > 60 mg/dL and < 130 mg/dL, respectively.[18]

The determination of plasma glucose was performed using the commercial kit GLUCOSE PAP Liquiform (Labtest Diagnostica SA, Brazil). The reference values for fasting plasma glucose followed the recommendations of the American Diabetes Association (ADA), with appropriate values of fasting plasma glucose being below 100 mg/dL.[19]

Analysis of serum insulin was performed using the commercial kit COAT-A-Count® (Diagnostic Products Corporation®, USA). Normal insulinemia and hyperinsulinemia were considered in volunteers with fasting insulin < 9 μU/mL and > 9 μU/mL, respectively.[20]

Insulin resistance (IR) was estimated by calculating HOMA-IR (Homeostasis Model Assessment) according to Matthews et al.[21] IR values were considered as HOMA-IR ≥ 2.71.[22]

The QUICKI (Quantitative Insulin Sensitivity Check Index) calculation was used to evaluate IS, as proposed by Katz et al.[23] QUICKI values above 0.33 were considered adequate.[24]

Anthropometry assessment

Body weight and height were used to calculate BMI and to estimate the total energy expenditure (TEE), and consequently the total energy of the test meal. Body weight was assessed using digital platform scale (Filizola®) with an accuracy of 100 g and maximum capacity of 150 kg, and height was measured with the stadiometer of the same equipment with a scale of 0.1 cm. The volunteers were weighed with as little clothing as possible and barefoot.[25]

The WC was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape.[16]

Genotyping PPARγ2

Molecular analyses were performed in the Laboratory of Molecular Biology of Cancer, of Federal University of Rio de Janeiro.

Genomic DNA was extracted from samples of whole blood using a commercial kit (MasterPure™ Genomic DNA Purification Kit, Epicentre®, Biotechnologies) and stored at -20° C until the subsequent step.

Determination of the Pro12Pro genotype was performed using the polymerase chain reaction-restriction fragment-length polymorphism (PCR-RFLP) method as previously described[26], according the sequences available in the Gen Bank DNA AB005520.[27]

The sequences of PCR primers were: 5'-GCC AAT TCA AGC CCA GTC-3 'and 5'-GCC ATG TTT GCA

Table I
Usual dietary intake (energy and macronutrients) by groups

Variables	G1 (n = 17)[3]		G2 (n = 8)[4]		p-value[2]
	Mean	SD[1]	Mean	SD	
Energy (kcal)	2,234.27	748.79	1,928.77	726.76	0.35
Carbohydrates (%)	45.55	7.08	45.67	3.29	0.95
Protein (%)	18.12	3.95	17.88	3.77	0.89
Fat (%)	36.33	7.17	36.45	2.54	0.95
MUFA[5] (%)	13.35	3.53	13.08	1.80	0.84
SFA[6] (%)	12.20	3.27	13.62	2.59	0.29
PUFA[7] (%)	6.80	2.04	6.58	2.15	0.81

[1]Standard deviation; [2]Difference between groups were tested with t-student unpaired test at 5% probability; [3]BMI between 40 and 45 kg/m^2; [4]BMI > 40 kg/m^2; [5]Monounsaturated fatty acids; [6]Saturated fatty acids; [7]Polyunsaturated fatty acids.

GAC AGT GTA TCA GTG AAG GAA TCG CTT TCC G- 3'. The cycling conditions were as follows: an initial denaturation at 95º C for 5 minutes, followed by 35 cycles of denaturing at 95º C for 30 seconds, annealing at 59º C for 30 seconds and extension at 72º C for 30 seconds. The final extension was continued at 72º C for 10 minutes and cooling to 4º C. The generated fragment was 267 bp (base pairs).

After enzymatic digestion of the PCR products (60ºC for 180 minutes) by Bst UI restriction endonuclease (New England Biolabs, Inc.), were generated fragments of 267 bp indicating the presence of wild-type homozygous genotype (Pro12Pro).[26]

Dietetic intervention

The TEE of each volunteer was estimated according to FAO/WHO[28] and the energy value of the meal was equivalent to a breakfast (15-20% of the TEE), with normal distribution of macronutrients (carbohydrates, proteins and lipids), containing 15% of PUFA (a mean of 88.6% and 11.4% of n-3 and n-6 PUFA, respectively), 10% of monounsaturated fatty acids (MUFA) and less than 10% of the saturated fatty acids (SFA). Calculations were based on recommendations for normal individuals.[18]

The meal consisted of carrot cake without frosting, toast, ricotta cheese plus soybean oil and skimmed milk with the following characteristics: 511.2 ± 50.4 kcal, being 50.0 ± 0.6% carbohydrates, 19.0 ± 1.7% proteins, 35.1 ± 0.5% lipids, 14.6 ± 0.5% PUFA, 9.3 ± 0.2% MUFA, 9.2 ± 0.4% of SFA and 5,485.9 ± 871.4 IU of vitamin A.

The analysis of the chemical composition of the meals was conducted in *Food Processor* program version 12 (Esha Research, Salem, USA, 1984).

Statistical analysis

Was used SPSS 11.0 for statistical analysis, considering significant $p < 0.05$.

To check the distribution of continuous variables (clinical[1], anthropometric[2] and biochemical[3]) was done the test of Kolmogorov-Smirnov (1: age; 2: body weight, BMI and WC, 3: serum insulin, plasma glucose, triglycerides, total cholesterol and fractions (HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol) and values of HOMA-IR and QUICK).

For the comparison between the means of the groups, the basic statistics of location (mean) and dispersion (standard deviation) were calculated.

Continuous variables presented normal distribution and was used the parametric Student *t* test for the comparison between groups. When the variance was less than 4, we used the Student *t* test for equal variances; otherwise, we applied the Student *t* test for different variances.

Results

Among women recruited, only 4% (n = 1) had the genotype variant (Ala), and therefore was excluded from the study.

The volunteers were divided into two groups according to BMI, with G1 (BMI between 40 and 45 kg/m^2) composed of 17 women (68%) and G2 (BMI > 45 kg/m^2) of 8 women (32 %), both morbidly obese.

Energy and macronutrients intake no differ between groups ($p > 0.05$), which shows homogeneity between them (table I).

The anthropometric and biochemical characteristics are presented in table II.

Body weight, BMI and WC differ between groups ($p < 0.05$). All volunteers showed excess visceral adiposity, represented by WC above 80 cm.[29]

G1 had normal fasting glucose (< 100 mg/dL) and G2 had impaired fasting glucose (101.6 ± 22.1 mg/dL)[19], with no difference between groups ($p > 0.05$). In G1 and G2, respectively, 29.4% and 50% of women had impaired fasting glucose, so this rise was more frequent in G2.

All women had a fasting insulin above the normal range (13.3 U/mL and 14.0 U/mL, G1 and G2, respec-

Table II
Anthropometric and biochemical variables (mean ± standard deviation) by groups

Variables	*G1 (n = 17)*[3]		*G2 (n = 8)*[4]		*p-value*[2]
	Mean	*SD*[1]	*Mean*	*SD*	
Age (years)	35.9	7.2	37.1	7.3	0.69
Weight (kg)	113.4	9.9	129.6	10.3	< 0.01*
BMI[5] (kg/m²)	42.4	1.5	49.5	4.8	< 0.01*
WC[6] (cm)	120.4	6.2	130.9	9.3	< 0.01*
Fasting glucose (mg/dL)	91.9	18.5	101.6	22.1	0.26
Glucose 1 h after diet (mg/dL)	106.6	31.8	104.5	30.0	0.88
Glucose 2 h after diet (mg/dL)	100.1	31.1	95.6	28.5	0.74
Fasting insulin (µU/mL)	13.3	7.5	14.0	5.2	0.82
Insulin 1 h after diet (µU/mL)	61.2	46.6	82.2	53.0	0.32
Insulin 2 h after diet (µU/mL)	45.5	22.0	46.2	28.9	0.95
HOMA-IR[7]	3.2	2.2	3.6	1.8	0.61
QUICKI[8]	0.34	0.05	0.32	0.03	0.30
Total cholesterol (mg/dL)	201.1	40.7	190.9	39.1	0.56
LDL-cholesterol (mg/dL)	128.8	33.3	129.3	35.0	0.98
HDL-cholesterol (mg/dL)	49.2	13.4	42.9	8.5	0.23
Triglycerides (mg/dL)	115.8	71.3	93.6	33.7	0.30

[1]Standard deviation; [2]Difference between groups were tested with t-Student unpaired test at 5% probability; [3]BMI between 40 and 45 kg/m²; [4]BMI > 40 kg/m²; [5]Body mass index; [6]Waist circumference; [7]Homeostasis Model Assessment; [8]Quantitative Insulin Sensitivity Check Index.
*p < 0,05.

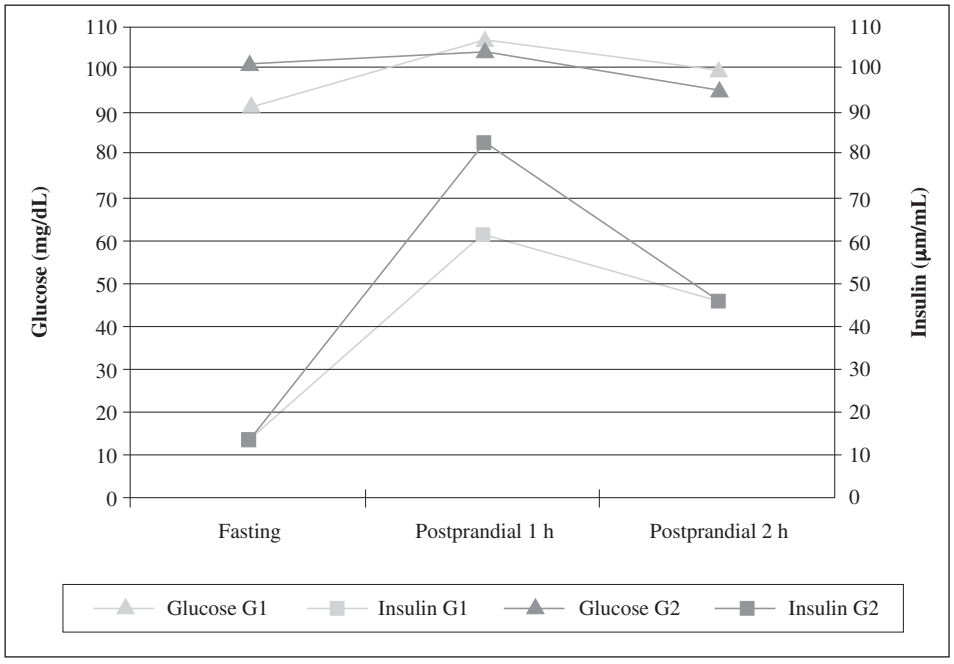

Fig. 1.—Plasma glucose (mg/dL) and serum insulin (µU/mL) concentrations, in fasting, 1 hour and 2 hours postprandial in G1 and G2.

tively)[20] and values of HOMA-IR greater than 2.71 indicating IR.[22] G1 had normal IS (QUICKI = 0.34 ± 0.05) and G2 showed low IS (QUICKI = 0.32 ± 0.03), however, there was no difference between groups ($p > 0.05$).

There was no difference in lipemia ($p > 0.05$) between groups and both showed normal mean values for triglycerides and LDL-cholesterol and low HDL-cholesterol concentrations.[18] In G1, total cholesterol was close to normal range (201.1 ± 40.7 mg/dL). In G1 and G2, 47.1% (n = 8) and 37.5% (n = 3) of the women, respectively, had values above the recommended, but there was no difference between groups ($p > 0.05$).

Figure 1 shows the variations in blood insulin and glucose in G1 and G2, at fasting, one and two hours after eating the test meal. In both groups, there was an

increase in blood glucose and insulin one hour after eating the test meal, followed by a fall two hours after, but there was no significant difference ($p > 0.05$) between groups (table II), however women with higher BMI (G2) showed a higher peak of insulin secretion one hour after eating the test meal.

Discussion

Obesity is considered a global epidemic and is associated with the genesis of other chronic diseases.[1] Studies relating adiposity and body fat distribution with IR contribute to the understanding of the relationship between obesity and other chronic diseases. Moreover, obesity is a complex disease of multifactorial origin and among the etiological factors involved, some genes are worth mentioning, such as the *PPARγ2*, whose effect on the IS remains controversial, justifying the genotyping of the women in this study.

In recent years, adipose tissue has become recognized as one of the principal responsible for several metabolic processes, with emphasis on energy balance and glucose homeostasis.[30,31] Among the genes and transcription factors that regulate adipogenesis, the nuclear receptor *PPARγ* has been detached.[3,6,30] Furthermore, *PPARγ* ligands have shown excellent antidiabetic activity although most of these transcription factors are found in adipose tissue and not in muscle.[30,32] The presence of genetic variant may alter its function, therefore, only carriers of the wild-type homozygous genotype were selected (Pro12Pro), making it possible to analyze the influence of adiposity on insulinemia and glucemia in morbidly obese women, excluding the possible influence of genotype on adiposity and IS.

The influence of adiposity in blood glucose and insulin and, consequently, in response to insulin, is already well established in literature.[31,33,34,35] However, there are few studies that control the possible influence of genes and diet in the variables studied. In the present study, the usual dietary intake did not differ between groups, excluding the possibility of the influence of habitual diet in the results.

Obesity is a major risk factor for the development of IR[33], the reason why the assessment of blood glucose and insulin levels was carried out according to BMI. As expected, G1 had lower body weight, BMI and WC, compared to G2.

The visceral adiposity is strongly associated with IR.[1] In the present study, both groups had excess visceral adiposity[29], however, it was higher in G2. G2 also showed slightly altered fasting glucose[19] and this change was more frequent in this group. G1 and G2 showed average values of fasting insulin, above 9 μU/mL, indicating a state of hyperinsulinaemia according to Sánchez-Margalet et al.[20] Additionally, both groups had IR, according Geloneze et al.[22] In contrast, when evaluating the IS, G1 showed normal value, but G2 had low SI. Thus, in spite of all women presenting morbid obesity, similar usual dietary intake and the same genotype for *PPARγ2*, the results suggest important metabolic differences with the increase of BMI and visceral adiposity.

PUFA is a natural ligant of the *PPARγ2*, then we evaluated the glucose and insulin concentrations on period postprandial after ingestion of this nutrient. We used a breakfast with about 15% of the TEE of this type of fat. In both groups, there was an increase in blood glucose and insulin one hour after eating the test meal, followed by fall two hours afterwards (fig. 1), despite the reduction in IS typically detected in women with morbid obesity.

We also observed that after eating the meal, the groups showed normal values of postprandial glucose (< 140 mg/dL).[19] G2 had a higher insulin secretion peak 1 hour after meal intake, compared to G1 (fig. 1), and IS below the reference value.

There is little information about the type of PUFA that is more potent for activating the *PPARγ*, furthermore the vast majority of studies did not specify the type of PUFA used. In few researches, different types of PUFA were tested simultaneously.[8,36] However, this study emphasizes the importance of controlling habitual dietary intake and the *PPARγ2* genotype, since the gene-environment interactions are associated with the genesis of obesity and other chronic diseases related to IR.

It is important to emphasize that the differences between the groups have great clinical and physiological significance in view of the importance of IR in the genesis of metabolic complications related to obesity.

Conclusions

It is possible to suggest that the body mass and the distribution of adiposity may have influenced in glycemia, whereas all women had the same genotype for *PPARγ2*, beyond the similarity observed in usual dietary intake between groups and of the same meal offered.

There was an increased risk for metabolic complications with the rise of body mass, although the volunteers had the same classification of obesity according to BMI. The increased risk may be associated with increased visceral adiposity, which is reflected in a higher frequency of hyperglycemia and lower IS.

Studies with other genes, concerning the expression of these with environmental factors, as well researches involving individuals with different genotypes for *PPARγ2*, are necessary to clarify other issues related to the etiology, prevention and treatment of obesity, emphasizing changes in environmental factors particularly dietary factors.

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